

UNITED STATES PATENT & TRADEMARK OFFICE

Examiner: ARNOLD, Ernst V. Art Unit: 1616

Re: Application of: KIM, In-San, *et al.*
Serial No.: 10/528,749
Filed: March 22, 2005
For: **BONE-FILLING COMPOSITION FOR
STIMULATING BONE-FORMING AND BONE-
CONSOLIDATION COMPRISING CALCIUM
SULFATE AND VISCOUS BIOPOLYMERS**

Confirmation No.: 8173

RESPONSE

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

December 3, 2007

Sir:

In response to the Office Action mailed on August 3, 2007, **remarks/arguments** begin on page 2 of this paper.

CERTIFICATE OF EFS-WEB TRANSMISSION
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December 3, 2007
LUCAS & MERCANTI, LLP

BY: 

Akiko Sakagami

REMARKS/ARGUMENTS

Reconsideration of the present application is respectfully requested.

A. STATUS OF THE CLAIMS

Claims 1, 3-5 and 7-8 are presented in the case for continued prosecution.

B. DECLARATION UNDER RULE 37 CFR 1.132

The Declaration under Rule 37 CFR 1.132 submitted on July 30, 2007 is resubmitted and incorporated as part of the response to the pending office action. Applicants submitted the Declaration shortly before the pending Office Action was issued. As such, Applicants believe that the Declaration was not taken into account when the Examiner issued the Office Action. Thus, Applicants respectfully request that the Declaration be considered as part of the response to the pending Office Action. Informality such as foreign characters found in Exhibit A attached to the Declaration was corrected.

C. SUMMARY OF THE INVENTION

The gel-type bone-filling compositions include (a) 20-80 weight % of a mixture containing 98-99 weight % of calcium sulfate, 0.3-1 weight % of CaCO_3 , 0.3-1 weight % of MgCO_3 and 0.5-1 weight % of $\text{CaCO}_3 \cdot \text{MgCO}_3$ and (b) 80-20 weight % of a viscous biopolymer. The inventive gel-type compositions advantageously remain where administered, and help stimulate bone-formation and bone-consolidation via efficient mineralization.

D. SUMMARY OF THE REJECTION

At pages 2-7 of the Office Action, the Examiner has rejected the subject matter of claims 1, 3-4 and 7 under 35 USC 103(a) as allegedly unpatentable over Petersen et al. (US Patent Application Publication 2002/0071827) in view of Liu (US Patent No. 5,281,265), Zimmermann (US Patent No. 6,692,563) and Walker (US Patent No. 4,795,475). The Examiner has alleged that "it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to make a bone filling composition with 0.3-1 weight % CaCO_3 , 0.3-1 weight % MgCO_3 and 0.5-1 weight % $\text{CaCO}_3 \cdot \text{MgCO}_3$, as suggested by Liu, Zimmermann and Walker, to the composition of Petersen et al. and produce the present invention".

At pages 7-9 of the Office Action, claims 1, 5 and 8 are also rejected under 35 USC 103(a) as allegedly unpatentable over Liu (US Patent No. 5,281,265) in view of Petersen et al. (US Patent Application Publication 2002/0071827), Zimmermann (US Patent No. 6,692,563) and Walker (US Patent No. 4,795,475). The Examiner has taken the position that "it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to make a bone filling composition of Liu wherein the ratio of calcium sulfate to carboxymethylcellulose is 50:50 and produce the instant invention".

It is respectfully submitted that the Examiner has not met the legal burden of sustaining a *prima facie* case of obviousness.

E. THE INVENTIVE GEL-TYPE BONE FILLING COMPOSITION IS NOT OBVIOUS

1. Petersen et al.

Petersen describes bone graft substitute compositions consisting essentially of (a) calcium sulfate, (b) a mixing solution such as water and inorganic salts, and (c) a plasticizing substance such as carboxymethylcellulose. The compositions of Petersen include three components, for example, (a) 80-120 parts by weight calcium sulfate, (b) 21-250 parts by weight water, and (c) 1-40 parts by weight plasticizing agent.

Petersen does not teach or suggest a bone filling composition including three salts of CaCO_3 : MgCO_3 : $\text{CaCO}_3 \cdot \text{MgCO}_3$ in a weight % ratio of 0.3-1: 0.3-1: 0.5-1. Applicants also wish to draw the Examiner's attention to item 9 of the attached declaration.

2. Liu

Liu describes surgical cements which harden into biocompatible hardened cements. The cements of Liu include (a) a cementing component such as calcium sulfate; (b) a setting component; (c) a biocompatible filler component; and (d) water. The Examiner states that "Liu et al. do teach and suggest mixtures of calcium carbonate and magnesium carbonate and other resorbable biocompatible materials (claim 16)". See page 6, last paragraph of the Office Action.

Contrary to the Examiner's position, no mixtures of embodiments listed in claim 16 of Liu as proposed by the Examiner and/or nowhere in Liu refer to including $\text{CaCO}_3 \cdot \text{MgCO}_3$ in a bone-filling composition as required in the inventive bone-filling composition. Liu at best

indicates possibilities of mixing CaCO_3 and MgCO_3 . It is respectfully urged that a mixture of CaCO_3 and MgCO_3 does not render nor correspond to $\text{CaCO}_3 \cdot \text{MgCO}_3$.

Unlike the inventive composition, Liu does not teach a bone-filling composition containing a mixture of calcium sulfate: CaCO_3 : MgCO_3 : $\text{CaCO}_3 \cdot \text{MgCO}_3$ in a weight % ratio of 98-99: 0.3-1: 0.3-1: 0.5-1. Applicants also wish to draw the Examiner's attention to item 10 of the attached declaration.

3. Zimmermann and Walker

Zimmermann describes a magnesium ammonium phosphate cement preparation. The cement of Zimmermann contains (a) calcium (Ca), magnesium (Mg) and orthophosphate (P) in a mixture in the ranges $1.00 < \text{Ca/P} < 1.50$ and $0 < \text{Mg/P} < 0.50$; (b) an ammonium salt; and (c) water and/or an aqueous solution. The cement according to Zimmermann can contain a powder mixture of α -TCP (tertiary calcium phosphate), β -TCP (tertiary calcium phosphate), $\text{MgHPO}_4 \cdot 3\text{H}_2\text{O}$, KH_2PO_4 and Na_2HPO_4 ; an ammonium salt; and water and/or an aqueous solution. See column 3, lines 24-34 of Zimmermann. The Examiner states that Zimmermann also discloses possibilities of admixing "other resorbable materials, such as: monetite CaHPO_4 , brushite $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$, calcite CaCO_3 and dolomite $\text{CaMg}(\text{CO}_3)_2$ ". See column 1, lines 63-65 of Zimmermann.

Walker describes an implant of which bone contacting surfaces contains biocompatible organic polymers substituted with oxyacid groups. Walker discloses that dolomite ($\text{CaMg}(\text{CO}_3)_2$) and other minerals have been found to exhibit osteophilic properties. See column 2, lines 60-65 of Walker.

Nowhere Zimmermann and/or Walker teach or mention the specific combination ratio of calcium sulfate and the three enumerated salts as required by the inventive composition. As such, neither Zimmermann nor Walker cures the compositions of Petersen and/or Liu to provide a bone-filling composition containing a mixture of calcium sulfate: CaCO_3 : MgCO_3 : $\text{CaCO}_3 \cdot \text{MgCO}_3$ in a weight % ratio of 98-99: 0.3-1: 0.3-1: 0.5-1 in combination with a viscous biopolymer.

4. The Inventive Gel-Type Bone-Filling Compositions Provide Unexpected, Superior Effects On Bone-Formation and Bone-Consolidation

Contrary to the Examiner's position, prior art including the cited references do not teach nor suggest that it would have been obvious to those of ordinary skill in the art to modify the compositions of Petersen and/Liu to arrive at the inventive compositions including calcium sulfate and the three salts, CaCO_3 , MgCO_3 and $\text{CaCO}_3 \cdot \text{MgCO}_3$ in a weight % ratio of 98-99: 0.3-1: 0.3-1: 0.5-1. Unlike the Examiner's position that artisans would have arrived at the claimed compositions according to the teachings of the references, such speculation at best invites one to experiment or provides an invitation to try various steps with hope that one would serendipitously stumble onto the inventive compositions. The Examiner's position is unfounded hindsight.

In the event that the Examiner takes that position that a *prima facie* case of obviousness has been made, it is urged that Applicants have provided sufficient evidence of unexpected results that would rebut the case in the declaration under 37 CFR 1.132 incorporated herein. The inventive compositions provide unexpected and superior results over art-known bone-filling cements, i.e. superior effect on bone formation and bone consolidation.

The effects of each of the inventive compositions ("Inventive Group" in the declaration) and art-known compositions ("Control Group") on bone-formation and bone-consolidation were measured by alkaline phosphatase activity ("ALP activity") assay in osteosarcoma cells. The art-known compositions do not contain a mixture of calcium sulfate, CaCO_3 , MgCO_3 and $\text{CaCO}_3 \cdot \text{MgCO}_3$ in the ratio as required in the inventive composition. Their relative compositions are described in Table 1 on page 7 of the declaration. Similarly, no compositions according to the cited references, alone or in combination contain calcium sulfate, CaCO_3 , MgCO_3 and $\text{CaCO}_3 \cdot \text{MgCO}_3$ as required by the claimed ratio. The comparison study was repeated three times.

The osteosarcoma cells treated with the inventive compositions showed 98-102 nmol/min/ μg ALP activities. On the other hand, the cells treated with the art-known compositions of Control Group showed 71-74 nmol/min/ μg ALP activities. The results are set forth in Table 2 on page 8 of the declaration.

The results indicate that the inventive bone-filling compositions have unexpectedly 1.35 to 1.37 times superior effects on bone-formation and bone-consolidation compared to those of

the art-known compositions. Considering a long period required in treatment associated with bone extension, any slight improvement of reducing the period of treatment via enhanced bone-formation and bone-consolidation is important. Especially, such improvements are much appreciated in adults as well as in minors because adults require substantially longer periods for bone-extension than minor patients. For example, it is advantageous that damages caused by bone fracture in nerve and muscle can be prevented from the enhanced bone-formation and bone-consolidation during the bone-extension treatment.

In order to provide the unexpected superior effects, it is urged that a mixture of calcium sulfate and the salts, CaCO_3 , MgCO_3 and $\text{CaCO}_3 \cdot \text{MgCO}_3$ as well as a viscous polymer such as carboxymethylcellulose (CMC) should be included in the specific amount ratio as required in the inventive compositions. As such, those skilled in the art would not have predicted that the specific amounts of the components, i.e., calcium sulfate: CaCO_3 : MgCO_3 : $\text{CaCO}_3 \cdot \text{MgCO}_3$ in a weight % ratio of 98-99: 0.3-1: 0.3-1: 0.5-1, would provide superior results in bone-formation and bone-consolidation.

For all the reasons set forth above, it is respectfully submitted that the claimed invention is not obvious over the prior art including Petersen, Liu, Zimmermann and Walker, whether taken alone or in any combination. Applicants respectfully urge that all of the currently examined claims patentably distinguish over the prior art. Reconsideration and withdrawal of the rejection is respectfully requested.

F. FEES

This response is being filed with a petition for a one-month extension of time. The required fee is being submitted via credit card authorization. Thus, no further fee is believed to be required. If, on the other hand, it is determined that any further fees are due or any overpayment has been made, the Assistant Commissioner is hereby authorized to debit or credit such sum to deposit account 02-2275.

Pursuant to 37 C.F.R. 1.136(a)(3), please treat this and any concurrent or future reply in this application that requires a petition for an extension of time for its timely submission as incorporating a petition for extension of time for the appropriate length of time. The fee associated therewith is to be charged to Deposit Account No. 02-2275.

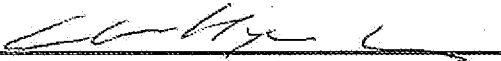
G. CONCLUSION

In view of the actions taken and arguments presented, it is respectfully submitted that each and every one of the matters raised by the Examiner have been addressed in this response and that the present application is now in condition for allowance.

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,

LUCAS & MERCANTI, LLP

By: 
Hyun Soon Cho
Recognition No. L0306

LUCAS & MERCANTI, LLP
475 Park Avenue South
New York, New York 10016
Phone: 212-661-8000
Fax: 212-661-8002